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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/885,799	LIN ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-13 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-13 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

RESTRICTION

1. Prior to setting forth the restriction requirement, it is pointed out that Applicants have presented the claims in improper Markush format. See Ex parte Markush, 1925 C.D. 126 and In re Weber, 198 USPQ 334. The claims are improperly joined as the claimed methods and detector systems require distinct oligonucleotides, derived from distinct HPV subtypes and from distinct regions of the HPV subtypes. A reference against one target oligonucleotide molecule would not be a reference against the other target molecule. Therefore, the restriction will be set forth for each of the various groups, irrespective of the improper format of the claims, because the claims do not recite proper species.

Claims 1-13 read on multiple patentably distinct inventions, each invention corresponding to a set of 2 oligonucleotides. Each oligonucleotide sequence is patentably distinct from each other and are unrelated because the sequences are derived from different HPV subtypes and from different regions of the HPV subtypes. Each of the oligonucleotide sequences is structurally unique and absent evidence to the contrary, each oligonucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.14. Because the claims require the detection of 2 HPV subtypes, Applicant is required to elect 2 oligonucleotides corresponding to a first and second HPV subtype.

Because these inventions are distinct for the reasons given above and have acquired a different status in the art as recognized by their divergent subject matter and because each invention requires different keyword and sequence searches that are not co-extensive, examination of these distinct inventions would pose a serious burden on the examiner and therefore restriction for examination purposes as indicated is proper.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

During a telephone conversation with Brian Buckwalter on March 27, 2002 a provisional election was made with traverse to prosecute the invention of claims 1-13 with respect to the invention that encompasses SEQ ID NO: 317, 318, 488 and 490. It is noted that claim 13 has been examined to the extent that it applies to methods utilizing oligonucleotides that hybridize to HPV 58, nucleotides 6608-7016 and HPV 70 nucleotides 6549-6963 since the primer pairs of 317/318 and 488/490 hybridize within these nucleotide regions. Affirmation of this election must be made by applicant in replying to this Office action. The subject matter of each of the additionally recited sequences is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

2. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Taiwan on April 5, 2001. It is noted, however, that applicant has not filed a certified copy of the 90110785 application as required by 35 U.S.C. 119(b).

3. The disclosure is objected to because of the following informalities:

The specification is objected to because the assigned SEQ ID NOs have not been used to identify each sequence listed, as required under 37 CFR §1.821(d). See, for example, pages 32 and 38 of the specification.

The specification includes non-English symbols which should be deleted and replaced with the correct English symbols (see, for example, pages 33 and 34).

4. Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5 are indefinite over the recitation of "hybridized" because it is not clear as to whether the oligonucleotides are already hybridized to the subtype DNAs or whether it is a property of the oligonucleotides that they are able to hybridize to the subtype DNAs. This rejection may be overcome by amendment of the claims to recite, for example, "wherein said first and second oligonucleotides respectively are complementary to deoxyribonucleic acids contained in a first subtype...".

Claims 4-5 are indefinite over the recitation of "the sequence group corresponding to" because this phrase lacks proper antecedent basis since the claims do not previously refer to a sequence group.

Claims 6-12 are indefinite over the recitation of "thereby said subtypes of human papilloma viruses contained in said sample are detected and identified" because it is not clear as to how the step of removing nonhybridized DNA results in the detection and identification of human papillomaviruses. The claims should be amended to recite an additional step in which sample DNA hybridized to the first or second oligonucleotides is detected as indicative of the presence of said subtypes of HPV in the sample.

Claim 13 is indefinite over the phrase "to show whether said subtype of human papilloma viruses contained in said sample" because it is not clear as to what is intended to be meant by this phrase. This rejection may be overcome by amending the claim to read, for example, "detecting a hybridization complex formed between said oligonucleotide and said DNA as indicative of the presence of said subtype of human papillomavirus contained in the sample".

Claim 13 is indefinite over the recitation of "said sequence specific to said subtype of human papillomaviruses is selected from the following" because the recited table lists HPV subtypes, Accession Numbers, and loci, but does not recite any particular sequences. Furthermore, it is unclear as to what is intended to be encompassed by the recited accession numbers. The sequences listed at, for example, a GenBank site are continuously updated and modified. Therefore, there is no single, fixed definition for the sequence presented as Accession No. NC 001525. To the extent that applicant can provide support for the sequences corresponding to each accession number, a new sequence listing should be provided and the claims should be amended to recite a specific sequence corresponding to each accession number. For example, Applicants may provide evidence in the form of a 132 declaration showing that at

the time of filing the recited accession numbers consisted of a particular sequence (and that particular sequence should be included in a newly filed paper and computer readable copy of the sequence listing).

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 5-9 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Doorn.

Van Doorn et al discloses methods for detecting specific HPV subtypes wherein the methods comprise amplifying nucleic acids contained in a sample with primers specific for HPV; contacting the amplified nucleic acids with a solid support which has attached thereto probes specific for at least 2 HPV subtypes; and detecting hybridization between said probes and amplified nucleic acids as indicative of the presence of a specific HPV subtype (see, for example, page 4 and Figure 10). In particular, the probes are specific for a single HPV subtype, including HPV 58 and HPV 70 (page 6). The probes are complementary to a region of HPV which includes a portion of the L1 gene that contains a high level of sequence variability, referred to therein as region D (page 7-8). The HPV subtype specific probes are immobilized onto a solid support as parallel lines to allow for the simultaneous detection of multiple HPV subtypes (pages 9 and 16). In reference to claims 2 and 5, Van Doorn teaches that the probe may be immobilized onto a nylon membrane or onto a chip (page 14). With respect to claim 4, the claims are inclusive

of oligonucleotides "complementary" to SEQ ID NO: 317, 318, 488 or 490. Because the term "complementary" has not been defined in the specification, this term is considered to be inclusive of oligonucleotides sharing any level of complementarity with the recited sequence. The HPV 58 and HPV 70 probes of Van Doorn share some level of complementarity with SEQ ID NO: 317, 318, 488 and 489 and thereby are considered to be encompassed by the claims. This aspect of the rejection may be overcome by amendment of the claim to recite, for example, "and oligonucleotides fully complementary thereto". With respect to claim 9, Van Doorn teaches that the HPV nucleic acid may be labeled with biotin (page 17). With respect to claim 13, the rejection applies to this claim based on the interpretation that the claim includes a method of detection wherein the HPV sequence is any sequence from HPV 58 or HPV 70 since the claim does not set forth a specific nucleotide sequence and does not clarify whether the "sequence specific to said subtype of human papillomaviruses" corresponds to the HPV subtype, the Accession No., the bp within the accession no., the loci, the last designated bp. Accordingly, Van Doorn teaches a detector comprising a first and second oligonucleotide bound to a carrier wherein the first and second oligonucleotide hybridize with a first and second subtype of HPV and methods for detecting and identifying a first and second subtype of HPV.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Doorn in view of Southern et al (5,700,637).

Van Doorn et al discloses methods for detecting specific HPV subtypes wherein the methods comprise amplifying nucleic acids contained in a sample with primers specific for HPV; contacting the amplified nucleic acids with a solid support which has attached thereto probes specific for at least 2 HPV subtypes; and detecting hybridization between said probes and amplified nucleic acids as indicative of the presence of a specific HPV subtype (see, for example, page 4 and Figure 10). In particular, the probes are specific for a single HPV subtype, including HPV 58 and HPV 70 (page 6). The probes are complementary to a region of HPV which includes a portion of the L1 gene that contains a high level of sequence variability, referred to therein as region D (page 7-8). The HPV subtype specific probes are immobilized onto a solid support as parallel lines to allow for the simultaneous detection of multiple HPV subtypes (pages 9 and 16). With respect to claim 4, the claims are inclusive of oligonucleotides "complementary" to SEQ ID NO: 317, 318, 488 or 490. Because the term "complementary" has not been defined

in the specification, this term is considered to be inclusive of oligonucleotides sharing any level of complementarity with the recited sequence. The HPV 58 and HPV 70 probes of Van Doorn share some level of complementarity with SEQ ID NO: 317, 318, 488 and 490 and thereby are considered to be encompassed by the claims.

With respect to claim 3, Van Doorn (page 50) teaches immobilizing the probes onto a nitrocellulose or nylon membrane, a microtitre plate, bead or onto a chip, but does not teach immobilizing the probes onto glass.

Southern teaches methods for simultaneously detecting multiple nucleic acids using probes attached to a solid support. Southern teaches that the probes may be attached to any type of solid support, including a glass plate (see, for example, column 1). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Van Doorn so as to have immobilized the probes onto a glass plate rather than a membrane, microtitre plate, bead or chip because this would have provided an equally effective means for immobilizing the probes and for allowing for the simultaneous detection of HPV subtypes.

With respect to claim 11, Van Doorn does not teach labeling the HPV nucleic acids with a fluorescent label. However, Southern teaches labeling probes with fluorescent moieties. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Van Doorn so as to have used a fluorescent label in place of biotin or digoxigenin in order to have provided an equally effective means for detecting the hybridization complex formed between the HPV nucleic acids and HPV subtype specific probes.

7. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Van Doorn in view of Bauer et al (U.S. Patent No. 5,639,871).

Van Doorn et al discloses methods for detecting specific HPV subtypes wherein the methods comprise amplifying nucleic acids contained in a sample with primers specific for HPV; contacting the amplified nucleic acids with a solid support which has attached thereto probes specific for at least 2 HPV subtypes; and detecting hybridization between said probes and amplified nucleic acids as indicative of the presence of a specific HPV subtype (see, for example, page 4 and Figure 10). In particular, the probes are specific for a single HPV subtype, including HPV 58 and HPV 70 (page 6). The probes are complementary to a region of HPV which includes a portion of the L1 gene that contains a high level of sequence variability, referred to therein as region D (page 7-8). The HPV subtype specific probes are immobilized onto a solid support as parallel lines to allow for the simultaneous detection of multiple HPV subtypes (pages 9 and 16). With respect to claim 4, the claims are inclusive of oligonucleotides "complementary" to SEQ ID NO: 317, 318, 488 or 490. Because the term "complementary" has not been defined in the specification, this term is considered to be inclusive of oligonucleotides sharing any level of complementarity with the recited sequence. The HPV 58 and HPV 70 probes of Van Doorn share some level of complementarity with SEQ ID NO: 317, 318, 488 and 490 and thereby are considered to be encompassed by the claims.

With respect to claim 10, Van Doorn (page 50) teaches detecting biotin labeled HPV nucleic acids using a streptavidin-alkalinephosphatase reaction system. Van Doorn does not teach detecting biotin labeled HPV nucleic acids using an avidin-alkalinephosphatase reaction

system. However, Bauer teaches detecting biotin-labeled HPV nucleic acids using an avidin-alkalinephosphatase detection system. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used avidin-alkalinephosphatase in place of streptavidin-alkalinephosphatase because this would have provided an equally effective means for detecting the hybridization between the HPV nucleic acids and HPV subtype specific probes.

8. Claims 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Doorn in view of Hyldig-Nielsen et al (U.S. Patent No. 5,888,733).

Van Doorn et al discloses methods for detecting specific HPV subtypes wherein the methods comprise amplifying nucleic acids contained in a sample with primers specific for HPV; contacting the amplified nucleic acids with a solid support which has attached thereto probes specific for at least 2 HPV subtypes; and detecting hybridization between said probes and amplified nucleic acids as indicative of the presence of a specific HPV subtype (see, for example, page 4 and Figure 10). In particular, the probes are specific for a single HPV subtype, including HPV 58 and HPV 70 (page 6). The probes are complementary to a region of HPV which includes a portion of the L1 gene that contains a high level of sequence variability, referred to therein as region D (page 7-8). The HPV subtype specific probes are immobilized onto a solid support as parallel lines to allow for the simultaneous detection of multiple HPV subtypes (pages 9 and 16). With respect to claim 4, the claims are inclusive of oligonucleotides "complementary" to SEQ ID NO: 317, 318, 488 or 490. Because the term "complementary" has not been defined in the specification, this term is considered to be inclusive of oligonucleotides sharing any level

of complementarity with the recited sequence. The HPV 58 and HPV 70 probes of Van Doorn share some level of complementarity with SEQ ID NO: 317, 318, 488 and 490 and thereby are considered to be encompassed by the claims.

With respect to claims 10 and 11, Van Doorn does not teach labeling the HPV nucleic acids with a fluorescent label and particularly does not teach using a Cyanine 5 label. Hylidig-Nielsen (column 10) teaches methods for labeling nucleic acids and specifically teaches labeling nucleic acids with the fluorescent label Cyanine 5, as well as labeling nucleic acids with biotin or digoxigenin. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Van Doorn so as to have labeled the HPV nucleic acids with Cyanine-5 because this would have provided an equally effective means for labeling and detecting HPV nucleic acids.

9. Claims 4, 5 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Doorn in view of Bauer et al (U.S. Patent No. 5,639,871) and Orth (U.S. Patent No. 5,981,173).

This rejection is based on the interpretation that the claims are inclusive of detectors and methods in which the first oligonucleotide is complementary to SEQ ID NO: 317 or 318 or hybridizes to a region that encompasses or flanks a portion of HPV 58 comprising SEQ ID NO: 317 or 318 and in which the second oligonucleotide is complementary to SEQ ID NO: 488 or 490 or hybridizes to a region that encompasses or flanks a portion of HPV 70 comprising SEQ ID NO: 488 or 490.

Van Doorn et al discloses methods for detecting specific HPV subtypes wherein the methods comprise amplifying nucleic acids contained in a sample with primers specific for HPV;

contacting the amplified nucleic acids with a solid support which has attached thereto probes specific for at least 2 HPV subtypes; and detecting hybridization between said probes and amplified nucleic acids as indicative of the presence of a specific HPV subtype (see, for example, page 4 and Figure 10). In particular, the probes are specific for a single HPV subtype, including HPV 58 and HPV 70 (page 6). The probes are complementary to a region of HPV which includes a portion of the L1 gene that contains a high level of sequence variability, referred to therein as region D (page 7-8). The HPV subtype specific probes are immobilized onto a solid support as parallel lines to allow for the simultaneous detection of multiple HPV subtypes (pages 9 and 16). With respect to claim 4, the claims are inclusive of oligonucleotides "complementary" to SEQ ID NO: 317, 318, 488 or 490. Because the term "complementary" has not been defined in the specification, this term is considered to be inclusive of oligonucleotides sharing any level of complementarity with the recited sequence. Van Doorn does not specifically teach probes comprising SEQ ID NO: 317, 318, 488 or 490 or probes which hybridize to a region comprising or flanking SEQ ID NO: 317, 318, 488 or 490.

Bauer teaches probes specific for HPV 58 wherein the probes consist of the sequence GCACTGAAGTAACTAAGGAAGG and sequences complementary thereto (see SEQ ID NO: 220 of Bauer). The complementary probe of Bauer is complementary to instant SEQ ID NO: 317 and 318 and hybridizes to a region of HPV 58 that encompasses SEQ ID NO: 317 and 318. Furthermore, the probe of Bauer differs from instant SEQ ID NO: 317 in that it is missing 2 5' nucleotides and contains 4 additional 3' nucleotides. The probe of Bauer also differs from instant SEQ ID NO: 318 in that contains 1 additional 5' nucleotide and 1 additional 3' nucleotide.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the probes of Bauer so as to have added or deleted nucleotides from the 5' or 3' terminus and to have thereby generated additional probes for specifically detecting HPV 58, including probes consisting of instant SEQ ID NO: 317 and 318. It would have been well within the skill of the art at the time the invention was made to have modified the probes of Bauer in such a manner since the sequences for HPV 58 and related HPV subtypes were well known in the art and because Bauer provides extensive guidance for modifying probes and for selecting additional probes specific for HPV 58.

Furthermore, with respect to HPV 70 probes, Orth teaches the complete sequence of the HPV 70 genome, including L1 sequences comprising instant SEQ ID NO: 488 and 490 (see SEQ ID NO: 11 of Orth). In addition, Van Doorn and Bauer each teach generating HPV subtype specific probes by comparing the L1 region of HPV subtypes and identifying those sequences within that are unique to a particular HPV subtype. The prior art also teaches the complete sequence of L1 for HPV subtypes. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated HVP 70 specific probes complementary to the L1 region in order to have to provided additional probes that specifically detect HPV. Again, it is noted that this aspect of the rejection as it pertains to HPV70 probes is applied to the claims to the extent that they are not limited to oligonucleotides of a specific sequence, but rather include probes which share some level of sequence complementarity with SEQ ID NO: 488 or 490 and include probes which hybridize to regions of HPV 70 comprising or flanking the sequences of SEQ ID NO: 488 or 490.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

April 3, 2002

Carla Myers

CARLA J. MYERS
PRIMARY EXAMINER